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Risk Factors for Pancreatic Cancer: A Case-Control Study Based on Direct Interviews

Debra T. Silverman*

Occupational Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland

The etiology of pancreatic cancer is poorly understood, partly because of the inconsistency of findings among case-control studies of pancreatic cancer. Because of the unfavorable prognosis for pancreatic cancer, many case-control studies have been based largely on interviews with next of kin, who are known to report less reliable information on potential risk factors than original respondents. The purpose of this study was to estimate the effects of speculative risk factors such as dietary/nutritional factors and alcohol drinking, as well as those of established risk factors such as cigarette smoking, diabetes mellitus, and family history of pancreatic cancer, on pancreatic cancer risk based solely on direct interviews.

This investigation was a population-based case-control study of pancreatic cancer diagnosed in Atlanta (GA), Detroit (MI), and ten New Jersey counties from August 1986 through April 1989. Direct interviews were conducted with 526 incident cases and 2,153 population controls.

This study revealed a significant interaction between body mass index and caloric intake that was consistent by both race and gender. Subjects with elevated body mass index and caloric intake had increased risk, whereas those with elevated values for one of these factors but not the other experienced no increased risk. This finding suggests that energy balance may play a major role in pancreatic carcinogenesis. Diabetes mellitus was also a risk factor for pancreatic cancer, as well as a possible complication of the tumor. Our data are consistent with a key role for hyperinsulinemia in pancreatic carcinogenesis, particularly among non-diabetics with an elevated body mass index. A three-fold risk of pancreatic cancer among first-degree relatives of affected individuals was apparent. An increased risk also was associated with a family history of colon, endometrial, ovary, and breast cancer, suggesting a possible link to hereditary non-polyposis colon cancer. Our findings support a causal role for cigarette smoking in pancreatic carcinogenesis. Alcohol

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*Correspondence to: Dr. Debra T. Silverman, Occupational Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Executive Plaza South, Room 8108, Bethesda, MD 20892. E-mail: silvermd@exchange.nih.gov

drinking at levels typically consumed by the general population of the United States did not appear to be a risk factor for pancreatic cancer, although heavy drinking may be related to risk, particularly in blacks. *Teratogenesis Carcinog. Mutagen. 21:7–25, 2001.*

Key words: cigarette smoking; alcohol consumption; dietary factors; diabetes mellitus; pancreatic neoplasm

INTRODUCTION

Cancer of the pancreas is the fifth leading cause of death from cancer in the United States, with nearly 30,000 deaths expected to occur in 2000 [1]. The incidence of pancreatic cancer in the United States is about 50% higher in blacks than among whites [2]. The etiology of pancreatic cancer is poorly understood, partly because of the inconsistency of findings among case-control studies of pancreatic cancer. Because of the unfavorable survival associated with this disease, many case-control studies have been based largely on interviews with next of kin [3–11], who are known to report less reliable information on potential risk factors than original subjects. The effect of misclassification of exposures by next of kin on quantification of the risk for potential risk factors is unclear but may be partly responsible for inconsistency of results among studies.

The present study is the largest population-based case-control study of pancreatic cancer to include only direct interviews. Our purpose was to estimate the effects of cigarette smoking, alcohol drinking, dietary/nutritional factors, medical conditions, and family history of cancer on pancreatic cancer risk based solely on direct interviews [12–15].

MATERIAL AND METHODS

This population-based case-control study was initiated simultaneously with case-control studies of three other malignancies that also occur excessively in blacks (i.e., esophagus, prostate, and multiple myeloma). One general population control group provided controls for all four types of cancer.

The case series included all cases of carcinoma of the pancreas (International Classification of Diseases for Oncology code = 157) newly diagnosed from August 1986 through April 1989 among 30–79-year-old residents of geographic areas covered by population-based cancer registries located in Atlanta (DeKalb and Fulton counties), Detroit (Macomb, Oakland, and Wayne counties), and New Jersey (ten counties). To ensure both the population-based nature of the case series and the completeness of case ascertainment, all cases with reported pancreatic cancer, regardless of the presence of tissue confirmation, were included initially. Because approximately 15% of the cases lacked tissue confirmation, an in-depth medical chart review was conducted to determine the accuracy of diagnosis. Based on this review, 5.5% of identified pancreas cancer patients were excluded as being "unlikely" to have pancreatic cancer. Further details of the chart review are reported in an earlier publication [16].

Because pancreatic cancer is a rapidly fatal disease, death was the major reason for nonresponse. Despite our emphasis on identifying and interviewing patients as quickly as possible (median time from diagnosis to interview: 7 weeks), 471 of the

1,153 patients initially identified for study died before the interview could be conducted. Of the 682 surviving patients identified for study, 526 (77%) cases were interviewed.

To determine the comparability of those who died to those who lived long enough to be interviewed, we conducted interviews with next of kin in a sample of 325 deceased cases. The next-of-kin interview was usually limited to broad categorical questions that next-of-kin respondents have been shown to answer reliably. For most questions, the pattern of responses from next-of-kin of deceased cases was similar to that for cases who were interviewed personally.

The control series was drawn from the general population of the study areas, frequency matching controls to the expected age-race-gender distribution of cases of all four types of cancer combined in each study area. Controls that were 30–64 years old were selected by random-digit dialing [17]. Of the 17,746 households telephoned, 86% provided a household census that served as the sampling frame for selection of controls under age 65 years. Of the 1,568 controls chosen from these households, we interviewed 1,227 (78%). Controls aged 65–79 years consisted of a stratified random sample drawn from the Health Care Financing Administration rosters of the population age 65 or older in each study area. Of the 1,232 older controls selected, we interviewed 926 (75%).

Interviews were typically conducted in the subject's home by a trained interviewer. Prior to the interview, written informed consent to participate in the study was obtained from each subject. The questionnaire was designed to elicit detailed information on smoking habits, alcohol intake, dietary and nutritional factors, medical conditions, family history of cancer, and socioeconomic status.

The effects of exposure on the risk of pancreatic cancer were quantified as an odds ratio (OR). ORs and 95% confidence intervals (CIs) were estimated by unconditional logistic regression analysis [18,19]. Statistical models included terms for exposure [i.e., cigarette smoking or alcohol consumption or diabetes mellitus (diagnosed at least 5 years prior to the diagnosis of cancer), cholecystectomy (occurring at least 2 years prior to the diagnosis of cancer), body mass index (BMI), total caloric intake], and matching factors (i.e., age at diagnosis/interview, race, gender, and study area), as well as potential confounding factors (i.e., typically the same as the exposures excluding the exposure of interest for that model). To test for linear trend, we computed the Wald statistic. The exposure variable was treated as continuous in the model by entering the median value for each level of the categorical variable among the controls. To test for interaction, we included a cross-product term in the model.

Interviewed subjects were excluded from analysis for the following reasons: presence of pancreatic cancer was unlikely (16 cases), presence of islet cell carcinoma (10 cases), no medical record available for review (6 cases), unsatisfactory interview (1 case and 7 controls), and missing data (12 cases and 11 controls). Thus, the analysis was based on first-person interviews with 481 "likely" cases with diagnosis of carcinoma of the exocrine pancreas and 2,099 population controls.

RESULTS

Cigarette Smoking

Cigarette smokers experienced a significant, 70% increased risk of pancreatic cancer compared with nonsmokers. The OR for current smokers was 2.0 (95% CI =

1.5–2.6), in contrast to an OR of 1.4 (95% CI = 1.1–1.9) for those who quit smoking more than 2 years prior to the interview.

The effect of smoking by gender and by race is presented in Table I. Men have a 50% higher incidence of pancreatic cancer than women [2]. Although both men and women experienced increased risk with increasing duration smoked, women had higher estimates of relative risk than men, among smokers of 20–39 years and 40 or more years. The interaction between gender and duration smoked was statistically significant ($P = 0.03$). Cigarette smoking accounted for 26% (95% CI = 12–48%) of pancreatic cancer in men and 29% (95% CI = 18–42%) of pancreatic cancer in women.

We also examined risk by race. Relative risk estimates for blacks and whites were almost identical at each level of duration smoked, except for the 20- to 39-year category, where the risk for whites was higher than that for blacks (OR = 2.2 and 1.3, respectively).

Alcohol Consumption

Table II shows risk of pancreatic cancer associated with total alcohol consumption. No association with ever drinking alcohol was apparent among men of either race. Black women experienced a nonsignificant, 50% increased risk of pancreatic cancer associated with ever having consumed alcohol, and white women experienced a marginally significant, 40% reduced risk.

TABLE I. Number of Cases and Controls and Odds Ratios (ORs) for Pancreatic Cancer According to Duration Smoked Cigarettes by Gender and Race*

	Years smoked				
Study subjects	0	<20	20–39	≥40	*P* for trend
Gender					
Men					
Number of cases	53	28	88	75	
Number of controls	418	174	399	337	
OR[a,b]	1.0	1.4	1.6	1.7	.009
95% CI		0.8–2.3	1.1–2.4	1.1–2.7	
Women					
Number of cases	96	13	63	63	
Number of controls	422	89	151	112	
OR[a,c]	1.0	1.1	2.0	2.8	<.0001
95% CI		0.3–1.3	1.3–3.0	1.8–4.3	
Race					
White					
Number of cases	90	29	110	77	
Number of controls	450	177	321	205	
OR[d]	1.0	1.1	2.2	2.3	<.0001
95% CI		0.7–1.8	1.5–3.1	1.5–3.4	
Black					
Number of cases	59	12	41	61	
Number of controls	390	86	229	244	
OR[d]	1.0	1.1	1.3	2.2	.003
95% CI		0.5–2.4	0.8–2.1	1.3–3.5	

*Base line is nonsmokers.
[a]ORs adjusted for age, race, area, alcohol consumption, and gallbladder disease.
[b]ORs also adjusted for income.
[c]ORs also adjusted for simple carbohydrate consumption.
[d]ORs adjusted for age, sex, area, income, alcohol consumption, and gallbladder disease.

TABLE II. Numbers of Cases and Controls and Odds Ratios (ORs) for Pancreatic Cancer According to Total Alcohol Consumption by Race and Gender

Total alcohol consumption	White				Black			
	Number of cases	Number of controls	OR[a]	95% CI	Number of cases	Number of controls	OR[a]	95% CI
				Men[b]				
Never drank	38	152	1.0		14	137	1.0	
Ever drank	128	589	0.9	0.6–1.4	66	462	1.0	0.5–1.9
Number of drinks/wk[e,f]								
Never drank	38	152	1.0		14	137	1.0	
1–<8	40	216	0.8	0.5–1.4	11	129	0.6	0.2–1.6
8–<21	39	204	0.8	0.4–1.3	24	164	1.2	0.5–2.6
21–<57	32	132	1.0	0.6–1.9	13	122	0.6	0.2–1.6
≥57	15	37	1.4	0.6–3.2	17	46	2.2	0.9–5.6
							(P=0.04)[d]	
				Women[c]				
Never drank	85	222	1.0		50	226	1.0	
Ever drank	56	201	0.6	0.4–0.97	44	120	1.5	0.9–2.7
Number of drinks/wk[e,f]								
Never drank	85	222	1.0		50	226	1.0	
1–<8	34	138	0.7	0.4–1.1	14	66	1.1	0.5–2.2
8–<21	15	52	0.4	0.2–0.9	17	34	1.8	0.8–4.0
≥21	7	11	0.9	0.3–3.0	13	20	2.5	1.02–5.9
							(P=0.03)[d]	

[a]ORs adjusted for age, area, cigarette smoking, gallbladder disease, and diabetes.
[b]ORs also adjusted for income.
[c]ORs adjusted for obesity.
[d]*P*-value for test of linear trend.
[e]1 drink = 1.5 oz. of hard liquor or 12 oz. of beer or 4 oz. of wine.
[f]Three cases and one control with missing information on amount of alcohol consumed were excluded from estimation of risk by amount consumed.

Significant trends in risk with increasing total alcohol intake were apparent for blacks but not whites (black men: $P = 0.044$; black women: $P = 0.029$). Although the trend was significant among black men, no evidence of a monotonic increase in risk was seen with increasing intake. Rather, risk was restricted to heavy drinkers, with those who drank at least 57 drinks per week having an OR of 2.2 (CI = 0.9–5.6) compared to 1.4 for white men (CI = 0.6–3.2). Among black women, the trend in risk with increasing total alcohol consumption was monotonic as well as significant. Black women who drank 8 to <21 drinks per week had an OR of 1.8 (CI = 0.8–4.0) and those who drank at least 21 drinks per week had an OR of 2.5 (CI = 1.02–5.9) compared to ORs of 0.4 and 0.9, respectively, for white women. The interactions between race and both heavy alcohol intake (≥ 57 drinks per week) in men and moderate-to-heavy intake (≥ 8 drinks per week) in women were statistically significant (men: $P = 0.04$; women: $P = 0.03$).

Despite the inclusion of terms for cigarette smoking in all models, we were concerned about residual confounding by smoking, a risk factor for pancreatic cancer and a strong correlate of alcohol drinking. To address this concern, we examined alcohol effects among lifelong nonsmokers when numbers permitted. For white nonsmokers, patterns of risk were similar to those observed for the total group of whites. For black nonsmokers, however, some alcohol effects were stronger than those observed for the total group of blacks.

Dietary/Nutritional Factors

Table III shows the independent effects of BMI, calories from food, and number of meals per day on risk of pancreatic cancer. For both men and women, the highest quartile of the BMI was associated with a 50% increase in risk. For men, the trend in risk with increasing BMI was significant ($P = .019$), although in the second and third quartiles there was little or no increased risk. For women, the trend was not significant, but those in the upper three quartiles experienced a 40–50% higher risk than those in the lowest quartile. For men and women combined, ORs for the lowest to the highest quartile were 1.0, 1.1 (95% CI = 0.8–1.5), 1.3 (95% CI = 1.0–1.8), and 1.6 (95% CI = 1.1–2.1), respectively, and this trend was significant ($P = .003$).

Among women, we observed a significant gradient in risk with increasing caloric intake ($P = .004$); women in the highest quartile of caloric intake experienced twice the risk of those in the lowest quartile. A significant trend in risk also was associated with number of meals per day among women ($P = .002$). Women who consumed only one meal per day had a 60% reduction in risk compared to those consuming three or more meals per day. Among men, similar patterns were seen. Men in the highest quartile of caloric intake had a nonsignificant, 40% increased risk compared to those in the lowest quartile, while men who consumed one meal per day had a nonsignificant, 40% reduction in risk. For men and women combined, ORs for the lowest to the highest caloric intake quartile were 1.0, 1.2 (95% CI = 0.9–1.7), 1.4 (95% CI = 1.0–1.9), and 1.7 (95% CI = 1.2–2.3) (P for trend = .001), and ORs for subjects who ate three or more meals per day, two meals per day, and one meal per day were 1.0, 0.8 (95% CI = 0.6–0.98), and 0.5 (95% CI = 0.3–0.96), respectively (P for trend = .006).

Pancreatic cancer risk is cross-classified by both BMI and total caloric intake in Table IV. Men and women above the median for both BMI and caloric intake experienced a significant, 70% increased risk compared to those below the median for both

TABLE III. Numbers of Cases and Controls and Odds Ratios (ORs) for Pancreatic Cancer According to Dietary Factors by Gender*

	Men				Women			
Factor	Number of cases	Number of controls	OR[a]	95% CI	Number of cases	Number of controls	OR[a]	95% CI
BMI[b,c,d]								
1	51	308	1.0		40	188	1.0	
2	39	310	0.8	0.5–1.3	54	187	1.4	0.9–2.3
3	55	311	1.1	0.7–1.7	57	180	1.5	0.9–2.4
4	73	302	1.5	1.0–2.3	62	192	1.5	0.9–2.5
			P = .019[g]				P=.129[g]	
Total calories from food[e,f]								
1	43	309	1.0		41	187	1.0	
2	49	308	1.0	0.6–1.6	54	185	1.4	0.8–2.2
3	60	307	1.2	0.8–1.9	50	188	1.4	0.9–2.3
4	66	307	1.4	0.9–2.1	68	187	2.0	1.2–3.2
			P = .112[g]				P = .004[g]	
No. of meals per day[e,f]								
≥3	141	707	1.0		145	427	1.0	
2	70	457	0.9	0.6–1.3	62	281	0.6	0.4–0.9
1	7	67	0.6	0.3–1.4	6	39	0.4	0.2–1.1
			P = .244[g]				P = .002[g]	

*BMI, body mass index; 95% CI, 95% confidence interval.

[a]ORs adjusted for age at diagnosis/interview, race, area, diabetes mellitus, gallbladder disease, cigarette smoking, alcohol consumption, income (men), and marital status (women).

[b]BMI, weight/height^2 for men; BMI, weight/height^{1,5} for women.

[c]Quartile outpoints for BMI:

Men: 17.35–23.13; 23.17–25.07; 25.09–27.18; ≥27.2 (kg/m^2).

Women: 20.49–27.54; 27.56–30.25; 30.30–34.21; ≥34.43 (kg/m^{1,5}).

[d]ORs also adjusted for calories from food.

[e]Quartile cutpoints for calories from food (kcal):

Men: 305–1361; 1363–1756; 1757–2167; ≥2168.

Women: 236–989; 991–1296; 1297–1621; ≥1628.

[f]ORs also adjusted for body mass index (women).

[g]P value for test of linear trend. All P values are two-sided and considered statistically significantly for P<.05.

TABLE IV. Odds Ratios (ORs) for Pancreatic Cancer According to Body Mass Index and Caloric Intake by Gender and Race*

	Total caloric intake							
	Men[b]		Women[b]		White[c]		Black[c]	
BMI	Low	High	Low	High	Low	High	Low	High
Low								
OR	**1.0**[a]	**0.9**	**1.0**[a]	**1.0**	**1.0**[a]	**0.9**	**1.0**[a]	**0.9**
95% CI	—	0.6–1.4	—	0.6–1.6	—	0.6–1.3	—	0.5–1.6
Number of cases/ Number of controls	46/308	44/310	51/190	43/185	65/284	62/305	32/215	25/191
High								
OR	**1.0**	**1.7**	**0.9**	**1.7**	**0.9**	**1.6**	**0.9**	**1.7**
95% CI	0.6–1.6	1.1–2.6	0.5–1.4	1.1–2.7	0.6–1.4	1.1–2.4	0.5–1.5	1.01–2.7
Number of cases/ Number of controls	46/309	82/304	44/182	75/190	56/250	94/250	34/241	63/245
	$P = .028$[d]		$P = 0.37$[d]		$P = .013$[d]		$P = 0.044$[d]	

*BMI, body mass index, calculated as kg/m^2 (men) or $kg/m^{1.5}$ (women); OR, odds ratio; 95% CI, 95% confidence interval.

[a]Baseline category is low BMI (below median—men: <25.2 kg/m^2; women: <30.3 $kg/m^{1.5}$), low caloric intake from food (below median—men: <1,757; women: <1,297). Odds ratio adjusted for age at diagnosis/interview, area, diabetes mellitus, gallbladder disease, cigarette smoking, alcohol consumption, income (men), and marital status (women).

[b]ORs also adjusted for race.

[c]ORs also adjusted for gender.

[d]Two-sided *P* value for test of interaction between body mass index and total caloric intake; *P* values are considered statistically significant for $P<.05$.

BMI and caloric intake. In contrast, men and women above the median for either BMI or caloric intake and below the median for the other factor had no increased risk. For both men and women, a significant interaction was found between BMI and caloric intake (P = .028 for men; P = .037 for women). For the total study group combined, we estimated risk by quartiles of both BMI and caloric intake. ORs for subjects in the highest two quartiles of BMI and caloric intake were significantly elevated relative to those in the lowest quartile of both BMI and caloric intake (quartile 3 of BMI/quartiles 3 and 4 of caloric intake: 2.1 [95% CI = 1.1–4.1] and 2.2 [95% CI = 1.2–4.2], respectively; quartile 4 of BMI/quartiles 3 and 4 of caloric intake: 2.2 [95% CI = 1.1–4.1] and 2.8 [95% CI = 1.5–5.2], respectively). No significantly elevated ORs were observed for other levels of BMI/caloric intake.

We also examined pancreatic cancer risk by the food groups. The only food group showing a significant trend in risk with increasing consumption in both men and women was cruciferous vegetables (men: P = .004; women: P = .002). Men and women in the highest (most frequent) quartile of cruciferous vegetable consumption (i.e., more than four times per week) experienced a significant, 50–60% decrease in risk compared to subjects in the lowest quartile (i.e., less than 1.5 servings per week). For men and women combined, ORs for the lowest to the highest quartiles of cruciferous vegetable intake were 1.0, 0.7 (95% CI = 0.5–0.9), 0.5 (95% CI = 0.4–0.8), and 0.5 (95% CI = 0.4–0.8) (P for trend = .0004). The associations for other food groups were not consistent among both men and women.

Medical Conditions

Diabetes mellitus. Table 5 shows risk of pancreatic cancer by length of the interval between diagnosis of diabetes and cancer. A significant positive trend in risk with increasing years prior to diagnosis of cancer was apparent (P = 0.016). Risk

TABLE V. Number of Cases and Controls and Odds Ratios (ORs) for Pancreatic Cancer According to History of Diabetes Mellitus and Cholecystectomy

Condition/intervention	Number of cases	Number of controls	OR[a]	95% CI
Diabetes mellitus[b]				
Interval between onset and diagnosis of cancer (years)				
No diabetes	398	1,846	1.0	
0–1	4	13	1.3	0.4–4.0
2–4	18	56	1.4	0.7–2.4
5–9	22	54	1.7	1.0–2.9
≥10	42	127	1.5	1.01–2.2
Cholecystectomy				
Interval between surgery and diagnosis of cancer (years)				
No cholecystectomy	345	1,941	1.0	
0–1	78	8	57.9	27.3–123.0
2–4	8	15	2.7	1.1–6.6
5–9	11	30	1.9	0.9–3.9
10–19	14	50	1.4	0.7–2.6
≥20	21	47	1.7	1.0–3.0

[a]Odds ratios adjusted for age at diagnosis/interview, race, gender, area, cigarette smoking, alcohol consumption, body mass index, and calories from food.
[b]Excludes three controls diagnosed with diabetes mellitus before age 20 years.

was slightly elevated for subjects with onset of diabetes within 1 year of diagnosis of cancer (OR = 1.3; 95% CI = 0.4–4.0). For subjects with longer intervals, risks were significantly increased, with ORs of 1.7 (95% CI = 1.01–2.9) and 1.5 (95% CI = 1.01–2.2) for those with onset of diabetes within 5–9 years and 10 or more years before the diagnosis of cancer, respectively. Treatment for diabetes and family history of diabetes did not appear to be related to risk of pancreatic cancer (data not shown).

Because obesity, an important risk factor for diabetes, was associated with pancreatic cancer risk in our study [14] as well as others [20–23], we cross-classified risk simultaneously by history of diabetes and BMI in Table VI. Within each level of BMI, diabetics had a higher risk than non-diabetics. In addition, a significant positive trend in risk with increasing BMI was apparent for non-diabetics ($P = 0.02$), but not for diabetics. These trends, however, were not significantly different from each other ($P > 0.05$).

Cholecystectomy. Table 5 presents risk following cholecystectomy according to the length of the interval to diagnosis of pancreatic cancer. Within one year prior to the cancer diagnosis, the risk associated with cholecystectomy was extremely high (OR = 57.9; 95% CI = 27.3–123.0). Although much diminished, risk remained elevated with increasing years prior to the diagnosis of cancer. Subjects who had a cholecystectomy 20 or more years prior to the cancer diagnosis had an OR of 1.7 (95% CI = 1.0–3.0).

Family History of Cancer

We also examined risk of pancreatic cancer by history of cancer among first-degree relatives. A significant 30% increased risk was associated with a family history of any cancer. Subjects with a family history of pancreatic cancer had a significantly elevated risk (OR = 3.2; 95% CI = 1.8–5.6). This risk was higher for those with pancreatic cancer in a sibling (OR = 3.6; 95% CI = 1.5–8.7) than in a parent (OR = 2.6; 95% CI = 1.2–5.4). Family history of pancreatic cancer was associated with a higher risk among long-term smokers (i.e., smokers for 20 or more years) (OR = 5.3; 95% CI = 2.1–13.4) than nonsmokers/short- and moderate-term

TABLE VI. Odds Ratio (ORs) for Pancreatic Cancer According to History of Diabetes Mellitus and Body Mass Index

	Body mass index[a,b]			
History of diabetes	1	2	3	4
No				
OR	1.0[c]	1.2	1.4	1.6
95% CI	—	0.8–1.6	1.1–2.0	1.2–2.2
Number of cases/number of controls	90/503	100/499	112/462	118/451
Yes[d]				
OR	2.7	1.7	1.8	2.2
95% CI	1.3–6.0	0.7–3.9	1.0–3.4	1.3–3.7
Number of cases/number of controls	11/22	8/28	16/55	29/76

[a]BMI, weight/height^2 for men; BMI, weight/height$^{1.5}$ for women.
[b]Quartile cutpoints for BMI (based on controls)—men: 17.4–23.1; 23.2–25.1; 25.2–27.2;>27.2(kg/m^2); women: 20.5–27.5; 27.6–30.2; 30.3–34.2; ≥34.4 (kg/m$^{1.5}$).
[c]Odds ratios adjusted for age at diagnosis/interview, race, gender, area, cigarette smoking, alcohol consumption, and calories from food.
[d]Excludes subjects diagnosed with diabetes less than 5 years prior to diagnosis of pancreatic cancer.

smokers (i.e., smoked for less than 20 years) (OR = 2.2; 95% CI = 1.0–7.9), although the interaction between familial predisposition and smoking was not statistically significant ($P > 0.05$).

With regard to family history of other cancers, risk of pancreatic cancer was significantly elevated for subjects with a family history of cancers of the colon (OR = 1.7) or ovary (OR = 5.3), and nonsignificantly elevated for those with a family history of cancers of the endometrium (OR = 1.5), breast (OR = 1.3) or liver (OR = 1.4).

DISCUSSION

Results of our study are consistent with those of previous studies, indicating that cigarette smoking, diabetes mellitus, and family history of pancreatic cancer are risk factors for pancreatic cancer. In addition, findings from the present study indicate that the following more speculative factors also may be pancreatic cancer risk factors: obesity, caloric intake, infrequent cruciferous vegetable consumption, cholecystectomy, and heavy alcohol consumption.

Cigarette smoking has been associated with increased risk of pancreatic cancer in at least 30 epidemiologic studies [24–27]. The dose-response relationship observed in these studies, however, was frequently weak. Our results also indicate that cigarette smoking is associated with increased risk of pancreatic cancer. The overall OR was 1.7 (95% CI = 1.3–2.2), with risk reaching 2.1 (95% CI = 1.6–2.9) for subjects who smoked for at least 40 years. Although the positive trends in risk with duration were both significant and consistent, the relatively small excess risk experienced by long-duration smokers suggests that cigarette smoke may be a weak to moderate pancreatic cancer carcinogen.

Our results suggest that alcohol drinking at the levels typically consumed by the U.S. general population is probably not a risk factor for pancreatic cancer. We observed no overall association between alcohol drinking and pancreas cancer risk, except among black women, who experienced a nonsignificant, 50% increased risk, and white women, who experienced a marginally significant, 40% reduction in risk. Trends in risk with increasing alcohol intake were only significant among blacks and only consistent among black women. Rather, our data suggest that heavy alcohol drinking may be a pancreatic cancer risk factor, particularly among blacks. Among men, blacks and whites who drank at least 57 drinks per week had ORs of 2.2 (95% CI = 0.9–5.6) and 1.4 (95% CI = 0.6–3.2), respectively. Among women, blacks who drank 8 to <21 drinks per week had an OR of 1.8 (95% CI = 0.8–4.0) and those who drank at least 21 drinks per week had an OR of 2.5 (95% CI = 1.02–5.9), but white women with the same levels of alcohol intake experienced no increased risk. The excess risk seen among heavy drinkers did not appear to be due to residual confounding by cigarette smoking. When alcohol effects were examined among lifelong nonsmokers, risk estimates for heavy drinkers were either similar or higher than those observed for the total study group.

Our findings are consistent with those of most previous studies that have found little or no support for a causal relation between regular alcohol drinking and pancreatic cancer risk [28,29]. It is plausible, however, that heavy alcohol drinking could be a risk factor for pancreas cancer. Chronic alcohol abuse is a known risk factor for chronic (calcifying) pancreatitis [30], which has been associated with increased pancreatic cancer risk in some reports [4,29,31]. At least nine studies have suggested

heavy drinkers may have an elevated risk [32–40], although an effect among heavy drinkers has not been seen in other studies [41–49].

Several possible explanations for the higher alcohol-related ORs in blacks compared to whites are apparent. Blacks and whites may differ in their alcohol drinking habits. For example, blacks may drink different brands of beer and hard liquor than whites. We were unable to evaluate race-specific risks by brand name because information on brand consumed was not obtained. Blacks also may be more susceptible to alcohol-induced pancreatic cancer than whites because of race-related differences (genetic or induced) in either alcohol metabolism or vulnerability to pancreatic tissue damage from heavy alcohol use. Additional research is needed to determine both the role of heavy drinking as a risk factor for pancreatic cancer and whether the risk of alcohol-related pancreatic cancer is greater in blacks than in whites.

Our findings indicate that BMI, caloric intake, and number of meals consumed per day may be related to the risk of pancreatic cancer. Obesity was associated with a significant, 60% excess risk that was consistent by both race and gender. A significant positive trend in risk with increasing caloric intake also was observed, with subjects in the highest quartile of caloric intake experiencing a 70% higher risk than those in the lowest quartile. In addition, a gradient in risk with increasing meals per day was apparent in both races and genders. Subjects who consumed one meal per day had a 50% reduction in risk compared to those having three or more meals per day.

Obesity was also associated with elevated risk in our study as well as in others, with relative risks ranging from 1.2 to 1.7 in some case-control investigations from the United States [20,23] and China [21], and in a cohort study from Denmark [22]. In contrast, a multi-national case-control study of pancreatic cancer [50–52] and some case-control studies in the United States [4,53,54] and Greece [55] have revealed no clear relationship to BMI. Caloric intake emerged as a risk factor in one U.S. study [54] and the multinational study [52], with a doubling of risk for subjects in the upper two quintiles of caloric intake compared to those in the lowest quintile. Energy intake, however, was not related to increased risk in two other studies where it was assessed [21,56]. The present study is the first to examine the relation between number of meals per day and pancreatic cancer risk.

The hypothesis that energy intake and number of meals per day are risk factors for pancreatic cancer is supported by data from animal studies. First, frequent food consumption may increase the amount of intraduodenal chyme, thus stimulating the duodenum to release the gastrointestinal hormone cholecystokinin (CCK). CCK, a major regulator of pancreatic growth and enzyme secretion [57,58], has been shown to act as a promoter of pancreatic carcinogenesis in rodents [59,60]. Second, energy restriction in rats has been found to inhibit pancreatic carcinogenesis [61,62], perhaps by decreasing levels of carcinogen-activating enzymes in the pancreas or decreasing tropic stimuli to the pancreas [63], although energy restriction does not appear to act as an inhibitor in hamsters [64]. A limitation of the present study is that we could not fully assess the effects of frequency and quantity of food consumption because information was not collected on snacking between meals.

Our study revealed for the first time a significant interaction between BMI and total caloric intake in relation to pancreatic cancer risk. This finding was noted in both genders and races. Subjects above the median for both BMI and caloric intake experienced a 70% higher risk than those below the median for both factors, rising to 180% for those in the highest quartile of BMI and caloric intake. In contrast, no

increased risk was found for subjects above the median for either BMI or caloric intake and below the median for the other factor, suggesting that energy balance may play a key role in pancreatic carcinogenesis. It may be that caloric intake in excess of that required to maintain energy balance (i.e., intake that leads to obesity) increases risk. In further studies evaluating the role of energy balance, it will be important to include data on physical activity, which was not obtained in our study.

We also found that frequent consumers of cruciferous vegetables (i.e., more than four servings per week) had a 50% reduction in risk. A protective effect associated with consumption of vegetables has been reported in at least ten previous studies of pancreatic cancer [23,38,65–72], with cruciferous vegetables being responsible for a 20–50% reduction in risk in studies conducted by Olsen et al. [38], Bueno de Mesquita et al. [66], and Ji et al. [67]. These findings are consistent with animal studies [73–76], indicating that constituents of cruciferous vegetables (including isothiocyanates, thiocyanates, and glucobrassicin, which when hydrolyzed produces indoles) have cancer-inhibiting effects. In particular, high doses of the antioxidant Oltipraz, a synthetic dithiolthione structurally similar to anticarcinogenic dithiolthiones found in oils derived from cruciferous vegetables, has been shown to inhibit pancreatic carcinogenesis in Syrian golden hamsters [77].

Our findings also indicate that diabetes mellitus is a risk factor for pancreatic cancer, as well as a potential consequence of pancreatic cancer. In particular, subjects diagnosed with diabetes at least 10 years prior to the diagnosis of cancer had a significant 50% increased risk, while a nonsignificant 30% increased risk was seen for subjects whose diabetes was detected within one year of the diagnosis of cancer.

The association between diabetes mellitus and pancreatic cancer has been evaluated in more than 30 studies [78–82], with most indicating a positive relationship. The critical question has been whether diabetes is a true etiologic factor or a consequence of pancreatic cancer during a prediagnostic stage.

Our study and others indicate that diabetes is a risk factor for pancreatic cancer. In 1995, Everhart and Wright [80] reported results of a meta-analysis of pancreatic cancer studies and found that diabetics diagnosed at least 5 years prior to the diagnosis of cancer had a relative risk (RR) of 2.0 (CI = 1.2–3.2). The pooled estimate from the cohort studies (RR = 2.6) was higher than that from the case-control studies (OR = 1.8). Our results are consistent with the pooled estimate for case-control studies.

The mechanism by which long-standing diabetes causes pancreatic cancer is uncertain. One possibility is that the relation is mediated by obesity, which is a risk factor for diabetes [83] and a risk factor for pancreatic cancer in the present study, as well as in previous studies [20–23]. We found, however, that diabetes was related to risk of pancreatic cancer within each quartile of BMI, most notably in the lowest BMI quartile (170% increased risk).

Another possible mechanism derives from experimental studies indicating that exposure to insulin promotes growth in human pancreatic cell lines [84]. Hyperinsulinemia is characteristic of both obesity and non-insulin dependent diabetes mellitus (NIDDM) [85], and may play a key role in pancreatic carcinogenesis [80]. Among non-diabetics, resistance to insulin action typically increases with increasing BMI, which results in hyperinsulinemia. Among diabetics, insulin levels are not strongly correlated with BMI but depend mainly on the degree of impaired B-cell function and hyperglycemia. The role of hyperinsulinemia in pancreatic cancer risk is consistent with our finding that the diabetes-related risk was not influenced by obesity,

while the risk associated with increasing BMI was seen only in non-diabetics. To further test this hypothesis will require a large-scale cohort study with repeated serum collections to determine if and when insulin levels become elevated prior to the onset of pancreatic cancer.

A third possible mechanism is based on experimental observations that peripheral insulin resistance is associated with increased cell turnover of the pancreatic islets, and stimulation of islet cell proliferation enhances pancreatic carcinogenesis in Syrian hamsters [86], which is considered an excellent animal model for human pancreatic carcinogenesis [87].

Last, the observed association between long-standing diabetes and pancreatic cancer may be due to confounding by a correlated variable. This explanation seems unlikely because the odds ratio for diabetes was adjusted for age at diagnosis/interview, race, gender, geographic area, cigarette smoking, alcohol consumption, BMI, and calories from food. Adjustment for other potential confounders had little or no impact.

Another key finding of our study was the positive association between cholecystectomy and pancreatic cancer risk. The 57-fold increased risk for subjects with cholecystectomy within 1 year of cancer diagnosis is probably an artifact resulting from either surgery prompted by symptoms of pancreatic cancer or inaccurate recall of patients regarding diagnostic work-up or treatment. Risk, however, remained elevated with increasing years prior to the diagnosis of malignancy, with a 70% excess risk among subjects with cholecystectomy 20 or more years prior to diagnosis of pancreatic cancer. These findings are consistent with most studies of cholecystectomy/gallbladder disease and pancreatic cancer. Of at least 17 studies conducted to date, 11 have been positive [23,34,68,88–95]. Few studies, however, have considered timing of the cholecystectomy/gallbladder disease in relation to pancreatic cancer. Of the 11 studies indicating a positive association, only four demonstrated an increased pancreatic cancer risk 5 or more years prior to the cancer diagnosis [23,88,93,94], while our study is the first to show an increased risk for subjects with a cholecystectomy at least 20 years prior to the cancer diagnosis, an interval too long to be considered prodromal to pancreatic cancer. A causal relation is further supported by experimental studies showing that cholecystectomy increases circulating levels of cholecystokinin (CCK), which is a promoter of pancreatic carcinogenesis in rodents as indicated previously [50,59]. Potential confounding by obesity, which is a risk factor for cholelithiasis and pancreatic cancer, was ruled out in our study.

The three-fold risk associated with a family history of pancreatic cancer in first-degree relatives resembles the risk estimates reported in case-control studies in the U.S. [5], Canada [96], and Italy [97]. In addition, the risk of pancreatic cancer associated with familial occurrence was highest among long-term cigarette smokers, suggesting an interaction between smoking and genetic predisposition. Subjects with a family history of pancreatic cancer who smoked for at least 20 years had a 5-fold risk compared to a 2-fold risk among nonsmokers and those who smoked for shorter durations. It is possible, however, that the differential familial risks are partly related to a tendency of smokers to have relatives who also smoke rather than to genetic predisposition. This possibility seems unlikely because there were no excesses associated with a family history of other smoking-related sites such as lung cancer. Alternatively, chance could not be reasonably excluded as an explanation for the differential familial risks by smoking status.

The elevated risk of pancreatic cancer extended to subjects with a family history of cancers of the colon (OR = 1.7), ovary (OR = 5.3), endometrium (OR = 1.5), and breast (OR = 1.3). These findings are consistent with the constellation of tumors associated with hereditary non-polyposis colon cancer [98,99]. This study is the first to report elements of the syndrome in a population-based study of pancreatic cancer, suggesting that the syndrome may occur more frequently than anticipated.

Our findings suggest important roles for both genetic predisposition and lifestyle/environmental factors in the etiology of pancreatic cancer. At this juncture, there is a critical need for studies to investigate the role of gene/environment interactions in pancreatic carcinogenesis.

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